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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/405,454	03/15/95	SULLIVAN	J 4249-0002-05

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EXAMINER	
SCHWADRON, R	
ART UNIT	**PAPER NUMBER**
1816	29

DATE MAILED: 06/19/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 4/15/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 40-49 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 40-49 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

15. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 4/15/97 has been entered. The amendment filed 1/27/97 has not been entered because applicant has not requested entry of said amendment.

16. Claims 40-49 are under consideration. Claims 40-49 have been amended.

17. Claims 40-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "antivenom" in claim 40. The specification and original claims read on antivenin not antivenom.

18. Claims 40-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "essentially free from contaminating Fc" in claims 40 and 45. The specification and original claims 27 and 29 do not recite that the claimed F(ab) are essentially free from contaminating Fc. They recite that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

19. Claims 40-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "said venom comprises more than one toxin" in claims 40 and 45.

20. Claims 41,43,46,48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "IgG(T)" as the antibody source for deriving the F(Ab). The specification and original claims discloses F(ab) derived from polyvalent IgG(T). However, the specification as originally filed does not disclose the scope of F(ab) derived from IgG(T) per se. For example, there is no disclosure in the specification as originally filed of the derivation of F(ab) from monoclonal IgG(T).

21. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

22. Claims 40-49 stand rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary (1977) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Applicants arguments in the amendment filed 4/15/97 have been considered and deemed not persuasive. Regarding applicants comments on pages 4-9 of the instant amendment, Coulter et al. teach that F(ab) which neutralizes snake toxin can be made and that said antivenin can work in vivo to neutralize snake toxin (see page 202, third paragraph). Thus, the Smith et al. reference

is relied on only to teach the advantages of using F(ab) in vivo, while Coulter et al. have already shown that F(ab) antivenin work in vivo to neutralize snake toxins. Regarding applicants comments, antisera against Crotalus toxin which contained antibodies to neutralize said toxin/toxins was already known in the art. Smith et al. teach that F(ab) are less immunogenic than the antibody from which they are derived (see page 395). Smith et al. teaches that,

"Relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance, and purified sheep digoxin specific Fab fragments have been utilized clinically for the reversal of advanced digoxin intoxication. This therapeutic approach is based on similar binding properties and the postulated lesser immunogenicity of Fab compared with IgG." (page 393). Thus, Smith et al. establishes the advantages of using F(ab) antivenin, while Coulter et al. establishes that said antivenin can neutralize snake venom toxin in vivo. Regarding applicants comments on pages 6-8 of the instant amendment, Coulter et al. establishes that F(ab) antivenin can neutralize snake venom toxin in vivo. Regarding the Faulstich et al. reference said reference teaches that monoclonal antibody against α amatoxin cannot be used to treat α amatoxin and that F(ab) obtained from said antibody also cannot be used to treat α amatoxin. Thus, the circumstances surrounding treatment of α amatoxin poisoning differ from treatment of snake venom because the use of antibody to treat snake venom is well known in the art and Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). Regarding applicants comments on pages 8 and 9 of the instant amendment about Balthasar et al., Balthasar et al. refer to α amatoxin, which is a toxin which cannot be treated with antibodies as shown by Faulstich et al. The circumstances surrounding treatment of α amatoxin poisoning differ from treatment of snake venom because the use of antibody to treat snake venom is well known in the art and Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). Furthermore, Balthasar et al. teach that the use of drug-binding antibodies and antibody fragments for the treatment of drug intoxication is well known. (see Abstract, last sentence). Thus, there are no negative teachings in Faulstich et al. or Balthasar et al. that would suggest that F(ab) antivenin could not be used to treat snake venom poisoning.

Regarding applicants comments on pages 9 and 10 of the instant amendment, it would have been obvious to a routineer that since antivenin antibody against Crotalus venom was known in

the art, and Coulter et al. establish that F(ab) antivenin can be used to treat snake venom derived toxin, that F(ab) antivenin against Crotalus venom could have been used to treat Crotalus venom. The antibody antivenin against Crotalus venom from which F(ab) would have been prepared was already known in the art and consisted of antibodies against toxins occurring in Crotalus venom. The efficacy of antibody against Crotalus venom was already known in the art. There is no evidence of record that suggests that it would have been unpredictable that F(ab) derived from said antibody could have been used as antivenin. Coulter et al. have already established that F(ab) antivenin can be used to treat snake venom derived toxin. Smith et al. teaches that F(ab) has a greater biodistribution in vivo than IgG from which the F(ab) were derived (see page 384, first paragraph). The greater volume of biodistribution of F(ab) results from the smaller size of F(ab) in distinction to the intact antibody. Thus, Coulter et al. teaches that F(ab) antivenin can neutralize snake venom derived toxin and Smith et al. teaches that F(ab) have greater biodistribution such that the F(ab) would be more likely that intact antibody to distribute to the proper anatomical location to encounter snake venom that was administered. Thus, there is no reason to doubt that F(ab) could be used to treat snake venom poisoning. The F(ab) antivenin against Crotalus venom would have been derived from art known antibody against Crotalus venom which is polyclonal and contains antibodies against various toxins found in Crotalus venom.

Regarding the Smith declaration and Sullivan declaration, both declarations ignore the fact that Coulter et al. teaches that F(ab) antivenin can neutralize snake venom derived toxin. Furthermore, regarding the use of F(ab) antivenin, Sullivan (1986) teaches that:

"Recently, investigations have resulted in the production of active Fab and Fab2 fragments from the IgG(T)(Sullivan et al. 1984). Studies with these fragments are ongoing and may be a promising new immunotherapeutic agent for human envenomations."(page 56, first column). Sullivan (1986) also teaches that:

"Since Fab fragments have the same affinity for antigen as IgG, they are better suited for toxin and drug neutralization as well as for enhancing their elimination." (page 50, column 1). Thus, Sullivan (1986) establishes that the art recognized that there would have been a reasonable expectation of success that the claimed invention would have worked.

Regarding applicants comments about long felt need on page 13 of the instant amendment, there is no evidence submitted that the FDA recognized a need for improved antivenin or that the FDA recognized that the claimed invention was an improved antivenin. Furthermore, Sullivan

(1986) establishes that F(ab) antivenin was known in the art as of 1986. The antibody preparation that is disclosed in the FDA documents is an ovine preparation which is not disclosed in the instant application, which only discloses horse derived antibody preparations. The scope of the ovine preparation is not commensurate in scope with the scope of the claimed compositions (eg. horse derived or no limitation on source of F(ab)). Thus any results found with the ovine preparation are not pertinent to the scope of the claims under consideration. Regarding the Smith et al. reference, the use of a reference in a rejection under 35 U.S.C. § 103 is irrelevant to the issue of the scope of unexpected results that can overcome a rejection under 35 U.S.C. § 103. With regards to the clinical study depicted in paragraphs 12 and 13 of the Smith declaration, there is no disclosure in the specification of TAb001, or a F(ab) fragment containing antisera against Vipera berus. None of the claims under consideration read on antivenin against Vipera berus. Regarding applicants comments about Smith et al., the F(ab) preparation taught by Coulter et al. is not derived from ovine antisera.

23. Claims 43,44,48,49 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons elaborated in the previous Office Action.

Claim 43 is substantially duplicative of claim of claim 41, because both claims read on the same product. Claim 44 is substantially duplicative of claim of claim 42, because both claims read on the same product. Claim 48 is substantially duplicative of claim of claim 46, because both claims read on the same product. Claim 49 is substantially duplicative of claim of claim 47, because both claims read on the same product.

Regarding applicants comments on page 11 of the instant amendment, the claims under consideration in this rejection are identical.

24. Claims 45-49 remain rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Regarding applicants comments, Coulter et al. teach that: "Fab fragments of IgG have been used in enzyme immunoassay instead of IgG (Kato et al. 1976). EIAs of higher sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme." (page 199, first paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced the claimed F(ab) fragments because Coulter et al. teaches that: "EIAs of higher sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme" and therefore a routineer would have produced the F(ab) against Crotalus venom for use in EIAs to detect said venom.

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

26. Claims 40-49 are rejected under 35 U.S.C. 102(a) as being anticipated by Sullivan et al. (Veterinary and Human Toxicology).

Sullivan et al. teach the claimed inventions (see Abstract).

27. Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 180 at (703) 305-7939.

28. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00. The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ms Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1800

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1816
June 18, 1997